

Alterations Of Stress-Responsive Neuropeptide Function In Depressive Syndromes: Clinical And Pathophysiologic Implications

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Major depression is an illness whose principal feature is an alteration in mood, but which is also characterized by changes in behavioral and physiologic functions characteristically affected by acute stress, such as arousal mechanisms and feeding and sexual behavior. Recent clinical observations suggest that there may be multiple subsyndromes included within the overall category of depressive disorders. Hence, while the classical form of depression, melancholia, tends to be associated with evidence of pathologic activation of stress response systems, such as anxiety, agitation, insomnia, and anorexia, other subgroups of patients manifest symptoms suggestive of a pathologic inactivation of these systems, including fatigue, lethargy, hypersomnia, and hyperphagia (so-called "atypical depression"). Accordingly, our group has examined the potential role of stress-responsive neurohormonal systems in the pathophysiology of these depressive syndromes. We have focused on corticotropin-releasing hormone (CRH), which is a principal regulator of glucocorticoid secretion from the adrenal glands, and may be a principal effector of the central components of the stress response as well. We have also examined the potential role of arginine vasopressin (AVP), which exerts synergistic effects with CRH on pituitary ACTH secretion and in certain behavioral paradigms, and of somatostatin (SRIH), which may be inhibitory to CRH and/or ACTH secretion and which in turn may be stimulated by CRH in the central nervous system.

In patients with melancholic depressions, whom we and others have found to have increased cortisol secretion particularly during the evening hours (when its secretion is low or undetectable in controls), we have obtained several independent lines of evidence suggesting hypersecretion of CRH into both the hypophyseal-portal and central nervous systems. Additional data showing dose-related stimulation of hypothalamic CRH, and plasma ACTH and cortisol secretion by local anesthetics such as procaine, which induce limbic kindling in experimental animals, suggest that stimulation of central CRH secretion may play a role in the progressively-exacerbating longitudinal course of affective disorders. This idea is compatible with our finding of a positive correlation between age and CSF CRH levels in depressed patients, but not in control subjects, and with preclinical data suggesting that CRH itself can induce limbic seizures and may play a role in stimulant-induced behavioral sensitization. Cerebrospinal fluid (CSF) levels of CRH decline significantly in patients with major depression during treatment with the antidepressant agent fluoxetine or following electroconvulsive therapy (ECT). CSF AVP levels also decline significantly during fluoxetine treatment.

In contrast to the evidence suggesting hypersecretion of CRH in melancholic depression, CSF CRH levels are reduced in patients with Cushing's disease, who develop an atypical depressive syndrome associated with lethargy, weight gain, and daytime somnolence. These reduced CSF CRH levels in Cushing's disease appear to reflect an appropriate suppression of centrally-directed CRH due to the peripheral (i.e., pituitary) source of their hypercortisolism. In addition, patients with Cushing's disease show decreased CSF levels of AVP and SRIH compared to controls, suggesting that modulation of these peptides by peripheral hypercortisolism may account for the reductions in centrally-directed AVP and SRIH levels seen in previous studies of patients with major depression. Over groups of depressed patients not selected for the presence of melancholic or atypical features, an inverted U-shaped type of relationship may exist between central CRH secretion and other neuropeptides such as SRIH, which could account for the overlap of some clinical symptoms (such as depressed mood and decreased libido) across these putative subsyndromes of depressive illness.